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09/900,497	07/06/2001	Keith D. Allen	R-639	4128

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EXAMINER

QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	12

DATE MAILED: 09/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,497	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 August 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 16-20 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-15 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) Interview Summary (PTO-413) Paper No(s). _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

Art Unit: 1636

DETAILED ACTION

Claims 1-20 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I, II and II related, thus a search of all the groups can be made without serious burden. However, the Applicant does not offer any support for this assertion. This is not found persuasive because the inventions are patentably distinct for the reasons set forth of the record mailed on 7/2/02. A search of the subject matter of one invention would not be co-extensive with a search of the other invention, and therefore the additional search effort involved in searching all three inventions in a single application would be burdensome. Each invention is capable of supporting a separate patent.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 16 and 20 are withdrawn from consideration as being directed to non-elected subject matter. Claims 1-15 and 17-19 are currently under examination.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim is drawn to a construct comprising a screening marker. Since it's unclear how it is different from the "selection marker," claim 2 fails to limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a method of identifying an agent that modulates the NPY6 receptor gene expression and function by administering an agent to a NPY6 receptor gene knockout animal, and determine whether the expression or function of NPY6 receptor gene is modulated.

The guidance in the specification is limited in regarding this method. The specification does not teach a specific method in determining the expression or function of NPY6 receptor in a NPY6 receptor knockout animal. It is not known how to determine the expression or function of a gene that has already been knocked out. The prior art does not teach such a method either. In view of lack of guidance from both specification and prior art, one skilled in the art would have to engage in undue amount of experimentation to practice the method as claimed. If this aspect of rejection can be overcome, the scope of enablement rejection set forth below is applicable.

Art Unit: 1636

Claims 5-10, 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a disruption in the NPY6 receptor gene comprising the sequence set forth in SEQ ID NO:1, wherein both alleles are inactivated, and exhibiting phenotypic features such as increased agility or coordination as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression and/or function of NPY6 gene, and a cell isolated from the KO mouse, does not reasonably provide enablement for other transgenic and/or knockout animal comprising any disruption in any NPY6 receptor homolog gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in any NPY6 receptor homolog gene and for any cell comprising any disruption in a NPY6 receptor homolog gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Art Unit: 1636

Claims 5-10, 17-19 are drawn to a cell comprising a disruption in a NPY6 receptor homolog gene, a non-human transgenic animal comprising a disruption in a NPY6 receptor homolog gene, a cell from that transgenic animal, a method of producing the mouse with any disruption in the said gene, and a method of identifying an agent having an effect on a phenotype associated with the transgenic mouse. Thus, the nature of the invention is directed to transgenic animals and methods of using the transgenic animals in identifying agents that modulate gene expression.

Breadth of Claims:

In the instant case, the claims 5-10, 17-19 encompass any transgenic animal containing any disrupted allele for the gene that encodes any NPY6 receptor homolog. Further, the claims encompass any knockout mouse comprising any disruption in NPY6 receptor homolog gene and exhibiting the phenotypes of increased agility or coordination as compared to wild type mice. Further, the claims encompass any cell comprising any disruption in a NPY6 receptor homolog gene and encompass all cells capable of undergoing homologous recombination (specification page 9, line 1-3). The disruption, as disclosed in the specification (page 8, line 21-29) includes any insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover all animals that contain NPY6 receptor homolog gene disruption (page 9, lines 1-3).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 5-10, 17-19 is for a homozygous knockout mouse comprising a disruption in the NPY6 receptor gene that results in loss of function of the NPY6 receptor gene and exhibiting

Art Unit: 1636

phenotypic features such as increased agility or coordination as compared to wild type mice, a method of producing such a transgenic mouse. Thus the breadth of claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in any NPY6 receptor gene and includes any and all mutant forms, substitutions, deletions, or insertions in any NPY6 receptor gene (specification, page 7, lines 15-23).

Amount of guidance in the specification and Working Examples:

The specification discloses the use of a specific NPY6 receptor gene as set forth in SEQ ID NO:1 in producing a homozygous transgenic knockout mouse, wherein the knockout mouse exhibits phenotypic changes that include increased agility or coordination as compared to wild type mice.

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine NPY6 receptor gene of SEQ ID NO:1 wherein the disruption results in loss of function of the NPY6 receptor gene. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding NPY6 receptor, as claimed in the claims 5-15, 17-19. Further, the specification does not teach how to make and use any cell comprising any type of disruption in a NPY6 receptor gene as claimed. The scope of claims 5-10, 17-19 thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine NPY6 receptor wherein the knockout mice exhibit increased agility or coordination. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous NPY6 receptor gene knockout mouse comprising a disruption in the NPY6 receptor gene comprising the sequence set forth in SEQ ID NO:1 and fails to disclose the phenotypes of any and all KO animals with a disruption in NPY6 receptor gene. Thus, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1,

lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the invention while being enabled for a homozygous knockout mouse containing two disrupted alleles for the gene comprising the sequence set forth in SEQ ID NO:1 and encodes a NPY6 receptor, does not extend the predictability of the invention to other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not always predictable. For example, Jacks et al. (1992) describe Rb KO mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the NPY6 receptor gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The only species in which such

Art Unit: 1636

technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538).

Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1. Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice of the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a homozygous knockout mouse comprising a disruption in the NPY6 receptor gene as set forth in SEQ ID NO:1 and exhibiting phenotypic features of increasing agility or coordination as compared to wild type mice, and a method of producing such a transgenic mouse.

Claims 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.gov).

The specification does not provide or point to a written description of the genus of NPY6 receptor genes recited in the claims. Claims 17 is directed to a transgenic and/or knockout mouse containing NPY6 receptor or homology gene disruption. However, the specification only describes a single species of a transgenic, knockout mouse of the type claimed, wherein the said disruption is within the gene that encodes a specific NPY6 receptor gene comprising the SEQ ID NO:1. The specification fails to teach other “homolog” of SEQ ID NO:1 from other species of animals besides mice, or “homolog” that has the same function as murine NPY6 receptor. In analyzing whether a written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claims encompass the whole genus of ‘NPY6 receptor or homolog genes’ and include any and all transgenic animals that contain any altered allele for the gene that encodes a NPY6 receptor or a homology thereof. Thus for the claims to meet the written description requirement, other representative species of “NPY6 receptor homolog genes”, should be described by their complete structure or by other relevant identifying characteristics, in the specification.

Art Unit: 1636

Next, then, it is determined if a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, no identifying characteristics are provided for the genus of NPY6 receptor homolog gene disruptions recited in the claims. Thus the limited information in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed genus of NPY6 receptor homolog gene disruptions. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of "NPY6 receptor or homolog genes".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? Where is the screening marker located in the construct? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene.

Regarding claim 2, the term "screening marker" renders the claim indefinite because it is unclear what term encompasses. In other words, it is unclear how a "screening marker" differs from the "selection marker" recited in claim 1.

Art Unit: 1636

Regarding claim 9 , the word “derived” renders the claim indefinite because the nature and number of derivative processes is unknown.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Weinberg et al. (1996, JBC Vol. 271, pages 16435-16438).

The claims are drawn to an NPY6 receptor gene-targeting construct and a method of making said construct. The claims are further drawn to a cell and a transgenic animal comprising a disruption in an NPY6 receptor, and a method of producing a transgenic mouse comprising a disruption in an NPY6 receptor gene by homologous recombination using the target construct.

Mansour et al. teach a strategy for targeted disruption of the hprt gene and proto-oncogene int-2 in mouse embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cell carrying non-selectable, targeted gene mutation at loci of interest, and therefore provides a model which can be used to produce homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3, third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the

Art Unit: 1636

generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from an hprt gene and an int-2 gene respectively, and a neo selection marker gene in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a NPY6 receptor target construct and knockout mouse.

Weinberg et al. teach that NPY has various biological function including effects on anxiety, cardiovascular function and feeding behavior; and NPY exerts these varied functions through the interaction with distinct receptor subtypes (see page 16435, 1st col., 1st and 2nd paragraph). Weinberg et al. teach that such receptors are classified into five subtypes based on their pharmacological properties consisting Y1, Y2, Y3, Y4, and "atypical" Y1 (see page 16435, 2nd col., lines 1-4). Weinberg et al. further teach the cloning of a new receptor subtype of NPY, Y5 (the sequence deposit number in Gene Bank, U58367 is same as the sequence in SEQ ID NO:1 of the specification although the specification name this receptor Y6), that is expressed specifically in kidney and within the discrete regions of hypothalamus (see Figure 3, and page 16438, 1st col., 2nd paragraph, lines 7-10). Weinberg et al. further teach the nucleic acid sequence encoding said receptor (see Figure 1, and Gene Bank U58367). Weinberg et al. also teach that inhibiting said receptor by antisense or antibody would help to address the precise physiological role of this receptor.

Based on the teaching of Weinberg et al. that each NPY subtype is involved in specific function of NPY, it would have been obvious to one of ordinary skill in the art to knockout the NPY6 receptor to study what biological role it plays in NPY signaling pathway. The ordinary artisan would have been motivated to knockout the expression of the NPY6 receptor gene in a mouse to study the role it plays in the complex biology of NPY and determine which NPY

Art Unit: 1636

signaling pathway(s) it mediates, as suggested by the teaching of Weinberg et al. The ordinary artisan would have had reasonable expectation of success for making such a knockout mouse because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired gene, and Weinberg et al., who teach the coding sequence of the mouse NPY6 receptor gene. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
September 7, 2002

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER